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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/926,299	10/09/2001	Yoshiya Gunji	212289US0PCT	4922

38108 7590 04/04/2006

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 04/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/926,299	GUNJI ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2005 and 17 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,7-10,12,13,16,17 and 20-31* is/are pending in the application.

4a) Of the above claim(s) *22-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,7-10,12,13,16,17,20,21 and 26-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/17/2006 has been entered.

[2] Claims 1-2, 5, 7-10, 12-13, 16-17, and 20-31 are pending in the application.

[3] Applicant's amendment to the claims, filed on 12/15/2005, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[4] Applicants' arguments filed on 12/15/2005 have been fully considered and are deemed to be persuasive to overcome some of the objections and/or rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Lack of Unity

[6] Claims 22-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable

generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1/14/2004.

[7] Claims 1-2, 5, 7-10, 12-13, 16-17, 20-21, and 26-31 are being examined on the merits.

Claim Objections

[8] Claim 5 is objected to as there is no conjunction joining the second occurrence of parts a) and b). It is suggested that applicant inserts "and" between the second occurrence of parts a) and b).

Claim Rejections - 35 USC § 112, Second Paragraph

[9] Claims 1-2, 5, 7-10, 12-13, 16-17, 20-21, and 26-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claims 1 (claims 12-13 and 26 dependent therefrom), 5 (claims 8-9 and 28-29 dependent therefrom), and 7 (claims 2, 10, 27, and 30-31 dependent therefrom) are indefinite in the recitation of "a protein…encoded by the DNA sequence comprising" specific nucleotides of a sequence identifier. See parts b) of claims 1, 5, and 7. A skilled artisan would recognize that, in view of the transitional phrase "comprising," the recited DNA can include additional nucleotides at its 5'- and 3'-ends. Thus, the term at issue encompasses numerous DNAs. However, it is unclear as to *the* DNA sequence of the

numerous DNAs that is specifically referenced by the claim. Consequently, it is unclear as to the scope of proteins that are encompassed by the claims. It is suggested that applicant clarify the meaning of the claims.

[b] Claims 1 (claims 12-13 and 26 dependent therefrom), 5 (claims 8-9 and 28-29 dependent therefrom), and 7 (claims 2, 10, 27, and 30-31 dependent therefrom) are confusing in the recitation of "a protein encoded by the DNA sequence depicted in a nucleotide sequence comprising nucleotide numbers..." See parts a) of claims 1, 5, and 7. It is unclear from the claims and the specification as to *the* intended DNA sequence that is referred to by the phrase "the DNA sequence depicted in a nucleotide sequence..." In the interest of advancing prosecution, the examiner has interpreted the phrase "a protein encoded by the DNA sequence depicted in a nucleotide sequence comprising nucleotide numbers..." as meaning "a protein encoded by a DNA comprising nucleotides..." It is suggested that applicant clarify the meaning of the claims by, for example, replacing the phrase "a protein encoded by the DNA sequence depicted in a nucleotide sequence comprising nucleotide numbers ..." with "a protein encoded by a DNA comprising nucleotides..."

[c] Claims 17 and 21 are confusing in the recitation of "the nucleotide sequence of the nucleotide numbers..." See parts a) and b) of claims 17 and 21. It is unclear from the claims and the specification as to *the* intended nucleotide sequence of the recited nucleotide numbers that is referred to by the phrase "the nucleotide sequence of the nucleotide numbers..." In the interest of advancing prosecution, the examiner has interpreted the phrase "the nucleotide sequence

of the nucleotide numbers..." as meaning "nucleotides..." It is suggested that applicant clarify the meaning of the claims by, for example, replacing the phrase "the nucleotide sequence of the nucleotide numbers..." with "nucleotides..."

[d] Claims 1 (claims 12-13 and 26 dependent therefrom), 5 (claims 8-9 and 28-29 dependent therefrom), 7 (claims 2, 10, 27, and 30-31 dependent therefrom), 16-17, and 20-21 are indefinite in the recitation of "inversion of one to 10 amino acids." Neither the specification nor the claims define the term "inversion" and it is unclear as to the meaning of the term in context of the claims. In this case, the term "inversion" has multiple meanings, *e.g.,* reversing the order of amino acids or inverting the configuration of an amino acid so that it is in a D-configuration, and it is unclear as to which of these interpretations – if any – is intended. Further, if applicant intends for the term "inversion" to be interpreted as meaning reversing the order of amino acids, because a single inversion necessarily requires two amino acids, is the term "inversion of one to 10 amino acids" meant to be comprehensive or not? For example, in an inversion of a first amino acid with a second amino acid, does the term "one to 10 amino acids" count the overall number of inverted amino acids (first and second), or count just the first amino acid? It is suggested that applicant clarify the meaning of the term "inversion of one to 10 amino acids."

[e] Claim 9 is indefinite in the recitation of "by introducing into cells a DNA sequence..." as it is unclear from the claims and the specification as to whether the "cells" are intended as being *M. methylotrophus* cells, or whether the "cells" are some other cells that, for example, cause a mutation to the recited

dihydrodipicolinate synthase and/or aspartokinase that result in an enhanced activity. It is suggested that applicant clarify the meaning of the claim.

Claim Rejections - 35 USC § 112, First Paragraph

[10] The written description rejection of claims 1-2, 5, 7-10, 12-13, 16-17, 20-21, and 26-31 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Initially, it is noted that a substantial portion of applicant's argument addressing the instant written description rejection (see paragraph bridging pp. 11-12) appear to be directed to the "undue experimentation" required to make and use the claimed invention. However, this is not the issue at hand. Instead, the issue is whether the specification adequately describes the claimed invention. To the extent applicants' arguments apply to the written description rejection, the arguments are addressed below.

Applicant argues methods for achieving enhancement dihydrodipicolinate synthase activity and/or aspartokinase activity in an *M. methylotrophus* host cell are well described in the specification, pointing to the following specific examples described in the specification: recombinant protein expression by inserting the encoding nucleic acid into an expression vector or the host cell chromosome and replacing a promoter with a known stronger promoter. According to applicant, in view of this disclosure, a skilled artisan would recognize that applicant was in possession of the claimed invention at the time of filing.

Applicant's argument is not found persuasive. With regard to claims 16 and 20, it is noted that MPEP 2111.01 states that "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." In this case, the examiner has broadly interpreted "an amino acid sequence of SEQ ID NO:6" of claim 16 to encompass a fragment of at least 2 amino acids of SEQ ID NO:6 and has broadly interpreted "an amino acid sequence of SEQ ID NO:10" of claim 20 to encompass a fragment of at least 2 amino acids of SEQ ID NO:10. In this case, the specification discloses only a single representative species of the recited genus of DNAs encoding a protein comprising as few as two amino acids of SEQ ID NO:6 or 10, *i.e.,* SEQ ID NO:5 or 9, respectively. Other than this single disclosed species, the specification fails to disclose any other species within the scope of the claims. In this case, the genus encompasses widely variant species, encompassing DNAs that encode a protein having dihydrodipicolinate synthase activity or aspartokinase activity. MPEP § 2163, which states, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." In this case, the single disclosed species fails to reflect the variation among the members of the genus.

With regard to claims 1-2, 5, 7-10, 12-13, and 26-31, the examiner maintains the position that the specification fails to adequately describe the claimed genus of *M. methylotrophus* strains, particularly with respect to the methods of enhancing dihydrodipicolinate synthase activity and/or aspartokinase activity and optionally enhancing the activities of a genus of aspartic acid

semialdehyde dehydrogenases, dihydrodipicolinate reductases, and/or diaminopimelate decarboxylases. While the examiner acknowledges applicant's cited methods for enhancing expression and activity of a polypeptide in a strain of *M. methylotrophus,* the claims encompass a strain of *M. methylotrophus* that has enhanced activity of dihydrodipicolinate synthase and/or aspartokinase activity and optionally enhanced activity of semialdehyde dehydrogenases, dihydrodipicolinate reductases, and/or diaminopimelate decarboxylases, homoserine dehydrogenases, homoserine kinases, and threonine synthases, wherein the activity is enhanced by *any* method, including, *e.g.,* mutation of the dihydrodipicolinate synthase and/or aspartokinase and optionally mutation of the semialdehyde dehydrogenase, dihydrodipicolinate reductase, diaminopimelate decarboxylase, homoserine dehydrogenase, homoserine kinase, and/or threonine synthase, mutation of endogenous promoter and enhancer sequences of a dihydrodipicolinate synthase and/or aspartokinase gene and optionally mutation of endogenous promoter and enhancer sequences of a semialdehyde dehydrogenase, dihydrodipicolinate reductase, diaminopimelate decarboxylase, homoserine dehydrogenase, homoserine kinase, and/or threonine synthase and/or altered activity of transcriptional regulatory factors that regulate dihydrodipicolinate synthase and/or aspartokinase biosynthesis and optionally altered activity of transcriptional regulatory factors that regulate semialdehyde dehydrogenase, dihydrodipicolinate reductase, diaminopimelate decarboxylase, homoserine dehydrogenase, homoserine kinase, and/or threonine synthase biosynthesis in *M. methylotrophus.* As such, the claims encompass widely variant

species and the specification's disclosure of an *M. methylotrophus* transformed with an expression vector comprising SEQ ID NO:5 (encoding dihydrodipicolinate synthase) or SEQ ID NO:9 (encoding aspartokinase), optionally further comprising an expression vector comprising SEQ ID NO:7, 11, and/or 13 fail to reflect the variation among the members of the genus.

Given the lack of description of a representative number of *M. methylotrophus* strains and DNAs as encompassed by the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[11] The scope of enablement rejection of claims 1-2, 5, 7-10, 12-13, 16-17, 20-21, and 26-31 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: According to applicant, many sequences of dihydrodipicolinate synthase and/or aspartokinase are known in the prior art and that based on sequence alignments one can determine which amino acids are tolerant to mutation, and thus, it would not require undue experimentation to make and use all nucleic acids and *M. methylotrophus* strains as encompassed by the claims. Applicant further argues that because the specification discloses 3 methods for enhancing protein activity and such methods are known in the prior

art, one of skill can determine methods for enhancing activities of the enzymes as encompassed by the claims without undue experimentation.

Applicant's argument is not found persuasive. With regard to claims 16 and 20, as noted above, the examiner has broadly interpreted "an amino acid sequence of SEQ ID NO:6" of claim 16 to encompass a fragment of at least 2 amino acids of SEQ ID NO:6 and has broadly interpreted "an amino acid sequence of SEQ ID NO:10" of claim 20 to encompass a fragment of at least 2 amino acids of SEQ ID NO:10. Thus, the claims broadly encompass any DNA that encodes a protein having dihydrodipicolinate synthase activity or aspartokinase activity. The specification discloses only a single working example of such DNAs, *i.e.,* SEQ ID NO:5 or 9, and fails to disclose sufficient guidance for making all DNAs that encode polypeptides with dihydrodipicolinate synthase activity or aspartokinase activity as encompassed by the claims. As noted in a prior Office action, the prior art acknowledges the high level of unpredictability in altering a protein's encoding sequence with an expectation of obtaining an encoded protein having a desired activity/utility. In view of the broad scope of the claims, the lack of guidance and working examples, the high level of unpredictability, and the amount of non-routine experimentation required to make all DNAs as encompassed by the claims, undue experimentation is required to make the full scope of the claimed invention.

With regard to claims 1-2, 5, 7-10, 12-13, and 26-31, the examiner maintains the position that the specification fails to enable all *M. methylotrophus* strains as broadly encompassed by the claims, particularly with respect to the

enhancements in dihydrodipicolinate synthase activity and/or aspartokinase activity and optionally enhancements to the activities of aspartic acid semialdehyde dehydrogenase, dihydrodipicolinate reductase, and/or diaminopimelate decarboxylase. While the examiner acknowledges applicant's three cited methods for enhancing expression and activity of a polypeptide in a strain of *M. methylotrophus,* the claims encompass a strain of *M. methylotrophus* that has enhanced activity of dihydrodipicolinate synthase and/or aspartokinase activity, optionally enhanced activity of semialdehyde dehydrogenase, dihydrodipicolinate reductase, diaminopimelate decarboxylase, homoserine dehydrogenase, homoserine kinase, and/or threonine synthase wherein the activity is enhanced by *any* method, including, *e.g.,* mutation of the desired protein itself, mutation of endogenous promoter and enhancer sequences of the desired protein, and/or altered activity of transcriptional regulatory factors that regulate the desired protein's biosynthesis in *M. methylotrophus.* Other than the three cited methods for enhancing a protein's activity, the specification fails to provide any additional guidance regarding methods for enhancing a protein's activity. As noted in a prior Office action, there is a high level of unpredictability in altering a bacterial strain or an encoding DNA sequence with an expectation of obtaining a strain or a DNA encoding a protein having a desired activity/utility. In view of the broad scope of the claims, the lack of guidance and working examples, the high level of unpredictability, and the amount of non-routine experimentation required to make all *M. methylotrophus* strains as encompassed

by the claims, undue experimentation is required to make the full scope of the claimed invention.

Claim Rejections - 35 USC § 102

[12] The rejection of claims 16 and 20 under 35 U.S.C. 102(b) as being anticipated by Kojima et al. (WO 95/16042; cited in the IDS filed 9/5/2003) is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Applicant argues the amino acid sequences of the dihydrodipicolinate synthase and aspartokinase polypeptides of Kojima et al. differ from SEQ ID NO:10 and 6, respectively, in more than 10 amino acids and thus, the DNA of claims 16 and 20 are not anticipated by Kokima et al.

Applicants' argument is not found persuasive. As noted above, the examiner has broadly interpreted "an amino acid sequence of SEQ ID NO:6" of claim 16 to encompass a fragment of at least 2 amino acids of SEQ ID NO:6 and has broadly interpreted "an amino acid sequence of SEQ ID NO:10" of claim 20 to encompass a fragment of at least 2 amino acids of SEQ ID NO:10. Thus, the claims broadly encompass any DNA that encodes a protein having dihydrodipicolinate synthase activity or aspartokinase activity. Kojima et al. teaches a DNA encoding a dihydrodipicolinate synthase or an aspartokinase polypeptide (pp. 65-66 and 70-72) and thus anticipates the claims.

Conclusion

[13] Status of the claims:

Claims 1-2, 5, 7-10, 12-13, 16-17, 20-31 are pending.

Claims 22-25 are withdrawn from consideration.

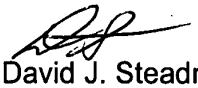
Claims 1-2, 5, 7-10, 12-13, 16-17, 20-21, and 26-31 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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Art Unit 1656